IN THE SPECIFICATION:

Please replace the paragraph beginning at page 6, line 1 with the following amended paragraph:

Currently more preferred prodrugs according to the invention are selected from the group consisting of:

1-Stearoyl-2-[3-(α–MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine,

1-Stearoyl-2-[3-(γ-dodecylate-α-MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine,

1-Stearoyl-2-[4-(α-MTX amido)-Butanoyl]-sn-Glycero-3- ~~Phosphatidylcholine~~ phosphocholine,

1-Stearoyl-2-[6-(α-MTX amido)-Hexanoyl]-sn-Glycero-3- ~~Phosphatidylcholine~~ phosphocholine,

1-Stearoyl-2-[8-(α-MTX amido)-Octanoyl]-sn-Glycero-3- ~~Phosphatidylcholine~~ phosphocholine,

1-Stearoyl-2-[8-(γ-dodecylate-α-MTX amido)-Octanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine,

1-Stearoyl-2-[3-(α-dodecylate-γ-MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine, and

1-stearoyl-2-[5'''-(2''-deoxy-5'-fluorouridine-5''-)-3''',3'''–dimethyl] glutaroyl-1'''-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine.

Please replace the paragraph at page 6, line 19 with the following amended paragraph:

Currently most preferred prodrugs are:

1-Stearoyl-2-[3-(α-MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine, and 1-Stearoyl-2-[3-(α-dodecylate-γ-MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine.

Please replace the paragraph beginning at page 10, line 7 with the following amended paragraph:

The lipophilicity of the lipid molecule is also affected by the nature of the phospholipid head group, denoted as R2 in the prodrug of the general formula I. The phospholipid moiety may be selected from, but is not limited to, the group consisting of phosphatidic acid, phosphocholine ~~phosphatidylcholine~~, phosphatidylethanolamine, phosphatidylinositol and phosphatidylserine.

Please replace the paragraph beginning at page 16, line 19 with the following amended paragraph:

Binding between the phospholipid and the MTX in these derivatives is via an ω-aminoacid at position-2 of lipid moiety. The synthesis pathway consists of six steps. Step 1 is protection of an amino group with a benzyloxycarbonyl resulting in the corresponding Z-amino acid. In step 2 the Z-amino acid is converted into the Z amino acid anhydride. Step 3 is synthesis of DP-amino acid, namely the formation of lipid derivative comprising the amino acid with protected amino group and a lyso-lecithin. Step 4 is de-protection, by hydrogenation, of the amino group of the amino acid. In step 5 the mixed anhydride of methotrexate or its γ-esters are prepared by reacting methotrexate (γ-esters) with isobutyl chloroformate in the presence of triethyl amine. In the last stage, step 6, the final product is obtained by reacting the mixed anhydride of methotrexate, or its ester, with 1-acyl-2-(ω-amino) acyl-Sn-glycero-3-~~phosphatidylcholine~~ phosphocholine in the presence of triethylamine as a catalyst.

Please replace the heading at page 19, line 22 with the following amended heading:

Stage 3. Preparation of 1-acyl-2- (Z-amino)acyl-sn-glycero-3-~~phosphotidylcholine~~ phosphocholine.

Please replace the paragraph beginning at page 19, line 24 with the following amended paragraph:

The anhydride of the corresponding Z-amino acid, 0.01 mol dissolved in 150 ml of freshly distilled chloroform, is introduced, under an inert atmosphere of argon, into a single-neck round-bottom flask (250 ml) equipped with a magnetic stirrer. To this solution 0.01 mol (1.22 g) 4-(dimethylamino)pyridine (DMAP) in 25 ml chloroform is added, followed by addition of a

suspension of 0.0056 moles lyso-lecithin in 50 ml of chloroform. The reaction mixture is vigorously stirred for 3-5 hours at room temperature. The lyso-lecithin dissolves and reaction mixture becomes transparent after about 2 hours of stirring. The reaction is monitored by TLC using silica gel 60 on ~~aluminium~~ aluminum sheet, the eluent is chloroform:methanol:water, 65:35:5, the indicator is a spray of the composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator followed by charring at 150^0C. The reaction is assumed to be complete and stopped when all the lyso-lecithin has disappeared. The reaction mixture is then transferred into a separating funnel and washed with a solution of 1% HCl (3x 50 ml), then with saturated solution of sodium bicarbonate (3x 50 ml) and finally with water (3x 50 ml). The obtained product in the organic solution is dried over sodium sulfate and then filtered. The solvent is evaporated at 30^0C in vacuo and the residue is washed with hexane and left to dry overnight under vacuum. The ~~resulted~~ resultant molecule 1-acyl-2-(Z-amino)acyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine is the main product of the reaction.

Please replace the paragraph beginning at page 20, line 30 with the following amended paragraph:

TLC analysis: Silica gel 60 on aluminium sheet. Eluent is chloroform/methanol/water (65:35:5 v/v). Indicator is a spray of the composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred at 100-150^0C.

The following are specific intermediate products obtained at the end of stage 3:

1-Stearoyl-2-{3'-[N-(Benzyloxycarbonyl)amino]}propanoyl-sn-glycero-3-~~phosphatidyl choline~~ phosphocholine.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.55

1-Stearoyl-2-{4'-[N-(Benzyloxycarbonyl)amino]}butanoyl-sn-glycero-3-~~phosphatidyl choline~~ phosphocholine.

White wax. Yield 70%. TLC analysis: One spot. R_f 0.55.

1-Stearoyl-2-{5'-[N-(Benzyloxycarbonyl)amino]}valeroyl-sn-glycero-3-~~phosphatidyl choline~~ phosphocholine.

White wax. Yield 65%. TLC analysis: One spot. R_f 0.55.

1-Stearoyl-2-{6'-[N-(Benzyloxycarbonyl)amino]}hexanoyl-sn-glycero-3-~~phosphatidyl choline~~ phosphocholine.

White wax. Yield 65%. TLC analysis: One spot. R_f 0.55.

1-Stearoyl-2-{8'-[N-(Benzyloxycarbonyl)amino]}octanoyl-sn-glycero-3-~~phosphatidyl choline~~ phosphocholine.

Please replace the paragraph beginning at page 21, line 3 with the following amended paragraph:

The obtained 1-stearoyl-2-{ω-[(N-Benzyloxycarbonyl)amino]}acyl-3-~~phosphatidyl-choline~~ phosphocholine (0.0025 mol) is dissolved in a mixture of 100 ml methanol and 5 ml acetic acid. The solution is introduced into round bottom double neck flask (200 ml) equipped with a magnetic stirrer, under an atmosphere of argon. Pd/C (0.5 g) is added to the solution and hydrogen is blown through the reaction mixture for 4 hours. The reaction proceeding is monitored by TLC analysis under the following conditions: silica gel 60 on aluminium sheet, eluent is the mixture of chloroform/methanol/water (65:35:5 v/v), indicator is a spray of the composition: p-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator and then charred at 100-150^{0}C.

Please replace the paragraph beginning at page 21, line 13 with the following amended paragraph:

The reaction assumed to be complete and hydrogenation is stopped after the corresponding 1-stearoyl-2-Benzyloxycarbonylaminoacyl-sn-glycero-~~phosphatidylcholine~~ phosphocholine has disappeared from the reaction mixture. The reaction mixture is then filtered through Wattman paper to remove the Pd/C, evaporated at 30^{0}C, under vacuum. The crude residue is washed with ether (3x 30 ml) and dried in vacuo overnight.

Please replace the paragraph beginning at page 21, line 19 with the following amended paragraph:

Conditions of the TLC analysis are the same as indicated above. The following are specific intermediate products obtained at the end of stage 4:

1-Stearoyl-2-(3-amino)propanoyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine, acetic acid.
White wax. Yield 70%. TLC analysis: One spot. R_f 0.2.
1-Stearoyl-2-(4-amino)butanoyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine, acetic acid.
White wax. Yield 70%. TLC analysis: One spot. R_f 0.2.
1-Stearoyl-2-(5-amino) valeroyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine, acetic acid.
White wax. Yield 65%. TLC analysis: One spot. R_f 0.2.
1-Stearoyl-2-(6-amino)hexanoyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine, acetic acid.
White wax. Yield 65%. TLC analysis: One spot. R_f 0.2.
1-Stearoyl-2-(8-amino)octanoyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine, acetic acid.
White wax. Yield 65%. TLC analysis: One spot. R_f 0.2.

Please replace the paragraph beginning at page 22, line 20 with the following amended paragraph:

A solution comprising the corresponding 1-stearoyl-2-ω-aminoacyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine of stage 4, acetic acid (0.589g., 0.9 mmol) and triethylamine (0.182g., 239 μl, 1.8 mmol) in 30 ml of dry freshly distilled chloroform is added dropwise to the reaction mixture of stage 5 for 30 min at -25^{0}C. The reaction mixture is stirred for additional one hour at -25^{0}C, and then for overnight at room temperature. The solvents are removed in evaporator under reduced pressure. The obtained residue is a thick viscous liquid. Diethyl ether (50 ml) is added to this liquid and the mixture is stirred. The product is gradually transformed into a yellow powder which is filtered and washed with diethyl ether (3x 20 ml). The crude product is purified by column chromatography as follows: 450 g. crude product is dissolved in 50 ml of methanol, followed by addition of 11.0 g. dry silica gel. The mixture is swirled, and then the volatile liquid is evaporated under reduced pressure to yield free-flowing yellow finely divided solid. The obtained solid is packed on top of a silica column (3x30 cm) (100g. silica gel per 1g of crude product). The product is eluted in succession with the solution MeOH:H_2O of variable composition: first fraction is 100:0 (v/v) (1L), second fraction is 99:1 (v/v) (1L), third fraction is 98:2 (v/v) (1L), and fourth fraction is 98:3 (v/v) (2L). The fractions, which contain the product (the determination is carried out by TLC analysis), are combined and the solvent is evaporated under reduced pressure. The obtained product (about 250 mg) is dissolved in mixture of methanol (10 ml) and chloroform (250 ml). The solution is washed with

1% HCl (3x 20 ml) and then with water (3x 20 ml). To achieve better separation of the aqueous and organic phases, isopropanol (about 25% of the volume of solution) is added. Isopropanol addition also promotes transition of the product into the organic phase. The organic layers are combined and dried over sodium sulfate. The sodium sulfate is filtered off and the solvent is distilled under reduced pressure. The obtained product is dried under vacuum for 3 hours.

Please replace the heading at page 23, lines 17-18 with the following amended heading:

1-Stearoyl-2-[3-(α-MTX amido)]-proponoyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine. $C_{49}H_{79}N_{10}O_{12}P$.

Please replace the heading at page 24, lines 1-2 with the following amended heading:

1-Stearoyl-2-[6-(α-MTX amido)]-hexanoyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine $C_{52}H_{85}N_{10}O_{12}P$.

Please replace the heading at page 24, lines 16-17 with the following amended heading:

1-Stearoyl-2-[3-(α- dodecylate-γ-MTX amido)]-proponoyl-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine. $C_{61}H_{103}N_{10}O_{12}P$.

Please replace the heading at page 25, lines 14-15 with the following amended paragraph:

Stage 2. Preparation of 1-acyl-2-ω-bromoalkylcarboxy-sn-glycero-3-~~phosphatidylcholine~~phosphocholine.

Please replace the paragraph beginning at page 25, line 16 with the following amended paragraph:

0.01 mol of the corresponding ω-bromoalkyl-carboxylic anhydride (obtained in stage 1) dissolved in 150 ml freshly distilled chloroform, is introduced, under an inert atmosphere of argon, into a single-neck round-bottom flask (250 ml) equipped with a magnetic stirrer. To this solution 0.01 mol (1.22 g) 4-(dimethylamino)pyridine (DMAP) in 25 ml chloroform is added, followed by addition of a suspension of 0.0056 moles lyso-lecithin in 50 ml chloroform. The reaction mixture is vigorously stirred for 3-5 hours at room temperature. The lyso-lecithin dissolves and reaction mixture becomes transparent after about 2 hours of stirring. The reaction is

monitored by TLC using silica gel 60 on aluminium sheet, the eluent is chloroform:methanol:water, 65:35:5, the indicator is a spray of the composition: 4-methoxybenzaldehyde (10 ml), absolute ethanol (200 ml), 98% sulfuric acid (10 ml) and glacial acetic acid (2 ml). The chromatogram is sprayed with the indicator followed by charring with hot air at 150^0C. The reaction is assumed to be complete and is stopped when all the lyso-lecithin has disappeared. The reaction mixture is then transferred into a separating funnel and washed with a solution of 1% HCl (3x 50 ml), then with saturated solution of sodium bicarbonate (3x 50 ml) and finally with water (3x 50 ml). The organic phase is dried over sodium sulfate and then filtered. The solvent is evaporated at 30^0C in vacuo and the obtained residue is washed with hexane and left to dry overnight under vacuum. The desired molecule 1-acyl-2-ω-bromoalkylcarboxy-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine is the main product of the reaction.

Please replace the paragraph beginning at page 26, line 22 with the following amended paragraph:

The procedure for the synthesis of DP-5FUdR compounds of the invention is exemplified below by the synthesis of the specific compound 1-stearoyl-2-[5'''-(2''-deoxy-5'-fluorouridine-5''-)-3''',3'''–dimethyl]glutaroyl-1'''-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine. The detailed description of the synthesis is described below. The products of the different stages of the synthesis are denoted as compounds **(1)** to **(5)**.

Please replace the heading at page 28, lines 18-19 with the following amended paragraph:

Stage 5. Preparation of 1-stearoyl-2-[5'''-(2''-deoxy-5'-fluorouridine-5''-)-3''',3'''–dimethyl]glutaroyl-1'''-sn-glycero-3-~~phosphatidylcholine~~ phosphocholine(5).

Please replace the paragraph beginning at page 29, line 10 with the following amended paragraph:

Cells were seeded at a density of 10^4 cells/ml in RPMI medium supplemented with 10% FCS in 96 well plates. The cultured cells were incubated, during their linear growth phase, in the presence and absence of various concentrations of MTX derivatives. The tested compounds were prepared as 1 mM stock in absolute ethanol or DMSO and were diluted into the medium. The

highest vehicle presence in the assay was 5% of the vehicle. After 72 hours at 37^0C the cytotoxic effect on the cells was estimated by using the colorimetric MTT assay (Mosmann (1983) J. Immunol Methods 65: 55-63) that measures mitochondrial reductase activity and serves for quantitative assessment of cellular viability. Drug concentration required for inhibiting the growth of 50% of cell population in culture over a 72 hour period incubation, is defined as EC_{50}. The EC_{50} values were calculated from dose response curves for each tested compound. The results of this screen are presented in Table 1.

The following MTX derivatives were tested:

α- dodecylate-MTX (**MTX-47**);

γ-dodecylate-MTX (**MTX-48**);

α- dodecylate-MTX-γ-dodecylate (**MTX-256**);

1-Stearoyl-2-[3-(α-dodecylate-γ-MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine (denoted **DP-MTX-71**);

1-Stearoyl-2-[3-(α-MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine (denoted **DP-MTX-93**);

1-Stearoyl-2-[4-(α-MTX amido)-Butanoyl]-sn-Glycero-3- ~~Phosphatidylcholine~~ phosphocholine (denoted **DP-MTX-129**);

1-Stearoyl-2-[6-(α-MTX amido)-Hexanoyl]-sn-Glycero-3- ~~Phosphatidylcholine~~ phosphocholine (denoted **DP-MTX-106**);

1-Stearoyl-2-[8-(α-MTX amido)-Octanoyl]-sn-Glycero-3- ~~Phosphatidylcholine~~ phosphocholine (denoted **DP-MTX-142**);

1-Stearoyl-2-[3-(γ-dodecylate-α-MTX amido)-Propanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine (denoted **DP-MTX-128**); and

1-Stearoyl-2-[8-(γ-dodecylate-α-MTX amido)-Octanoyl]-sn-Glycero-3-~~Phosphatidylcholine~~ phosphocholine (denoted **DP-MTX-127**).

The cytotoxic activity of the DP-MTX derivatives on the tested cells was compared to that of commercial MTX (Abitrexate®, from ABIC, Israel; or Sigma cat. # M 8407).

Please replace the paragraph beginning at page 43, line 18 with the following amended paragraph:

Experimental neointimal formation is induced by balloon injury in rats according to the following procedure. Male ~~Spraque~~ Sprague-Dawley rats (380-450 g) are anesthetized by inhalation of halothane and dinitric ~~oxyde~~ oxide. After the right common carotid artery and the right external carotid artery are exposed, a 2F Fogarty arterial embolectomy catheter (Baxter Healthcare, Santa Ana, CA) is inserted into the lumen of the right external carotid artery and is guided to a fixed distance (about 5 cm). The balloon is inflated with saline and is withdrawn at a constant rate back to a point proximal to the site of insertion. This procedure is repeated three times.